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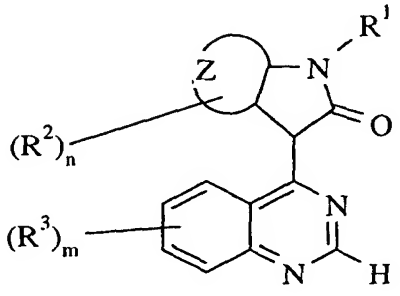


(I)

(57) Abstract: The present invention relates to a new use of oxindole derivatives of formula I, as a free base or pharmaceutically acceptable salts thereof, in the manufacture of a medicament for the prevention and/or treatment of dementia related diseases, Alzheimer's Disease and conditions associated with glycogen synthase kinase-3. Formula (I) wherein R^1, R^2, R^3, ring Z, m and n are as defined as in claim 1. The present invention further relates to a method of prevention and/or treatment of dementia related diseases, Alzheimer's Disease and conditions associated with glycogen synthase kinase-3, as well as a pharmaceutical composition for said use.

Use of oxindole derivatives in the treatment of dementia related diseases, Alzheimers Disease and conditions associated with glycogen synthase kinase - 3

FIELD OF INVENTION

The present invention relates to a new use of oxindole derivatives, as a free base or pharmaceutically acceptable salts thereof, in the manufacture of a medicament for the treatment and/or prevention of dementia related diseases, Alzheimer's Disease and conditions associated with glycogen synthase kinase-3. The present invention further relates to a method of treatment and/or prevention of dementia related diseases, Alzheimer's Disease and conditions associated with glycogen synthase kinase-3.

BACKGROUND OF THE INVENTION

Glycogen synthase kinase 3 (GSK3) is a serine / threonine protein kinase composed of two isoforms (α and β), which are encoded by distinct genes but are highly homologous within the catalytic domain. GSK3 is highly expressed in the central and peripheral nervous system. GSK3 phosphorylates several substrates including tau, ß-catenin, glycogen synthase, pyruvate dehydrogenase and elongation initiation factor 2b (eIF2b). Insulin and growth factors activate protein kinase B, which phosphorylates GSK3 on the serine 9 residue and inactivates it.

Alzheimer's Disease (AD) dementias, and taupathies.

AD is characterized by cognitive decline, cholinergic dysfunction and neuronal death, neurofibrillary tangles and senile plaques consisting of amyloid-β deposits. The sequence of these events in AD is unclear, but believed to be related. Glycogen synthase kinase 3β (GSK3β) or Tau (τ) phosphorylating kinase selectively phosphorylates the microtubule associated protein τ in neurons at sites that are hyperphosphorylated in AD brains. Hyperphosphorylated protein τ has lower affinity for microtubules and accumulates as paired helical filaments, which are the main components that constitute neurofibrillary tangles and neuropil threads in AD brains. This results in depolymerization of microtubules, which leads to dying back of axons and neuritic dystrophy. Neurofibrillary

tangles are consistently found in diseases such as AD, amyotrophic lateral sclerosis, parkinsonism-dementia complex of Gaum, corticobasal degeneration, dementia pugilistica and head trauma, Down's syndrome, postencephalatic parkinsonism, progressive supranuclear palsy, Niemann-Pick's Disease and Pick's Disease. Addition of amyloid-β to primary hippocampal cultures results in hyperphosphorylation of τ and a paired helical filaments-like state via induction of GSK3β activity, followed by disruption of axonal transport and neuronal death (Imahori and Uchida., J. Biochem 121:179-188, 1997). GSK3β preferentially labels neurofibrillary tangles and has been shown to be active in pre-tangle neurons in AD brains. GSK3 protein levels are also increased by 50% in brain tissue from AD patients. Furthermore, GSK3β phosphorylates pyruvate dehydrogenase, a key enzyme in the glycolytic pathway and prevents the conversion of pyruvate to acetyl-Co-A (Hoshi et al., PNAS 93:2719-2723, 1996). Acetyl-Co-A is critical for the synthesis of acetylcholine, a neurotransmitter with cognitive functions. Thus, GSK3β inhibition may have beneficial effects in progression as well as the cognitive deficits associated with Alzheimer's disease and other above-referred to diseases.

Chronic and Acute Neurodegenerative Diseases.

Growth factor mediated activation of the PI3K /Akt pathway has been shown to play a key role in neuronal survival. The activation of this pathway results in GSK3β inhibition. Recent studies (Bhat et. al., PNAS 97:11074-11079 (2000)) indicate that GSK3β activity is increased in cellular and animal models of neurodegeneration such as cerebral ischemia or after growth factor deprivation. For example, the active site phosphorylation was increased in neurons vulnerable to apoptosis, a type of cell death commonly thought to occur in chronic and acute degenerative diseases such as Alzheimer's Disease, Parkinson's Disease, amyotrophic lateral sclerosis, Huntington's Disease and HIV dementia, ischemic stroke and head trauma. Lithium was neuroprotective in inhibiting apoptosis in cells and in the brain at doses that resulted in the inhibition of GSK3β. Thus GSK3β inhibitors could be useful in attenuating the course of neurodegenerative diseases.

Bipolar Disorders (BD)

Bipolar Disorders are characterised by manic episodes and depressive episodes. Lithium has been used to treat BD based on its mood stabilising effects. The disadvantage of lithium is the narrow therapeutic window and the danger of overdosing that can lead to lithium intoxication. The recent discovery that lithium inhibits GSK3 at therapeutic concentrations has raised the possibility that this enzyme represents a key target of lithium's action in the brain (Stambolic et al., Curr. Biol. 6:1664-1668, 1996; Klein and Melton; PNAS 93:8455-8459, 1996). Inhibition of GSK3β may therefore be of therapeutic relevance in the treatment of BD as well as in AD patients that have affective disorders.

Schizophrenia

GSK3 is involved in signal transduction cascades of multiple cellular processes, particularly during neural development. Kozlovsky et al (Am J Psychiatry 2000 May;157(5):831-3) found that GSK3β levels were 41% lower in the schizophrenic patients than in comparison subjects. This study indicates that schizophrenia involves neurodevelopmental pathology and that abnormal GSK3 regulation could play a role in schizophrenia. Furthermore, reduced β-catenin levels have been reported in patients exhibiting schizophrenia (Cotter et al., Neuroreport 9:1379-1383 (1998)).

Diabetes

Insulin stimulates glycogen synthesis in skeletal muscles via the dephosphorylation and thus activation of glycogen synthase. Under resting conditions, GSK3 phosphorylates and inactivates glycogen synthase via dephosphorylation. GSK3 is also over-expressed in muscles from Type II diabetic patients (Nikoulina et al., Diabetes 2000 Feb;49(2):263-71). Inhibition of GSK3 increases the activity of glycogen synthase thereby decreasing glucose levels by its conversion to glycogen. GSK3 inhibition may therefore be of therapeutic relevance in the treatment of Type I and Type II diabetes and diabetic neuropathy.

Hair Loss

GSK3 phosphorylates and degrades β-catenin. β-catenin is an effector of the pathway for keratonin synthesis. β-catenin stabilisation may be lead to increase hair development. Mice expressing a stabilised β-catenin by mutation of sites phosphorylated by GSK3 undergo a

process resembling de novo hair morphogenesis (Gat et al., Cell 1998 Nov 25;95 (5):605-14)). The new follicles formed sebaceous glands and dermal papilla, normally established only in embryogenesis. Thus GSK3 inhibition may offer treatment for baldness.

Oral contraceptives

Vijajaraghavan et al. (Biol Reprod 2000 Jun; 62 (6):1647-54) reported that GSK3 is high in motile versus immotile sperm. Immunocytochemistry revealed that GSK3 is present in the flagellum and the anterior portion of the sperm head. These data suggest that GSK3 could be a key element underlying motility initiation in the epididymis and regulation of mature sperm function. Inhibitors of GSK3 could be useful as contraceptives for males.

DETAILED DESCRIPTION OF THE INVENTION

Compounds of general formula **I** are disclosed in WO 99/10349. The effect of the compounds on reducing antiangiogenic and/or vascular permeability in mammals has been investigated.

It has now suprisingly been found that the group of oxindole derivatives as decribed in WO 99/10349 are well suited for inhibiting glycogen synthase kinase-3. Said glycogen synthase kinase-3 inhibitors are suitable in the prevention and/or treatment of conditions associated with glycogen synthase kinase-3 in the central and peripheral nervous system. In particular, the compounds of the invention are expected to be suitable for prevention and/or treatment of especially dementia related diseases and Alzheimer's Disease.

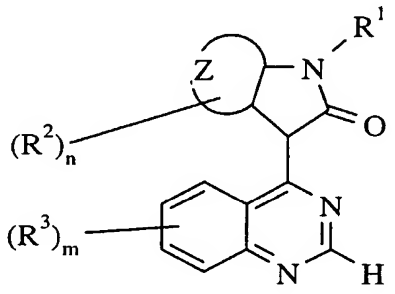
The dementia related diseases are selected from the group consisting of Frontotemporal dementia Parkinson's Type, Parkinson dementia complex of Guam, HIV dementia, diseases with associated neurofibrillar tangle pathologies, predemented states, vascular dementia, dementia with Lewy bodies, Frontotemporal dementia and dementia pugilistica.

The compounds of the invention are also expected to be suitable for prevention and/or treatment of amyotrophic lateral sclerosis, corticobasal degeneration, Down syndrome, Huntington's Disease, Parkinson's Disease, postencephelatic parkinsonism, progressive supranuclear palsy, Pick's Disease, Niemann-Pick's Disease, stroke, head trauma and other

chronic neurodegenerative diseases, Bipolar Disease, affective disorders, depression, schizophrenia, cognitive disorders, hair loss and contraceptive medication.

The compounds of the invention are further expected to be suitable for prevention and/or treatment of Mild Cognitive Impairment, Age-Associated Memory Impairment, Age-Related Cognitive Decline, Cognitive Impairement No Dementia, mild cognitive decline, mild neurocognitive decline, Late-Life Forgetfulness, memory impairment and cognitive impairment and androgenetic alopecia.

In the present invention GSK3 inhibitors of general formula **I** may be used in the manufacturing of a medicament for the treatment and/or prevention of conditions associated with glycogen synthase kinase-3:



(I)

wherein:

ring Z is a 5 or 6 membered heterocyclic ring containing 1 to 3 heteroatoms selected independently from O, N and S but not more than 2 nitrogen atom;

R^1 is hydrogen or C_{1-3}alkyl;

R^2 is hydroxy, halogeno, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, 2,2,2-trifluoroethyl, cyano, amino, nitro, C_{1-3}alkyl, C_{1-3}alkoxy, C_{1-3}alkanoyloxy, C_{2-4}alkanoyl, C_{1-4}alkanoylamino, C_{1-4}alkoxycarbonyl, C_{1-4}alkylthio, C_{1-4}alkylsulphinyl, C_{1-4}alkylsulphonyl, carbamoyl,*N*-C_{1-4}alkylcarbamoyl, *N*,*N*-di(C_{1-4}alkyl)carbamoyl, aminosulphonyl, *N*-C_{1-4}alkylaminosulphonyl, *N*,*N*-di(C_{1-4}alkyl)aminosulphonyl or C_{1-4}alkylsulphonylamino, or

R^2 is selected from one of the following groups:

1) R^4X^1, wherein X^1 is a direct bond, O, NR^5, C_{1-3}alkyl, C_{2-4}alkanoyl, $CONR^6R^7$, $SO_2NR^8R^9$ or SO_2R^{10} (wherein R^5, R^6 and R^8 each independently represent hydrogen or C_{1-2}alkyl and R^7, R^9 and R^{10} each independently represent C_{1-4}alkyl and wherein R^4 is linked to R^7, R^9 or R^{10}); and

R^4 is phenyl or a 5 or 6 membered heterocyclic group with one or two heteroatoms, selected independently from O, S and N, which heterocyclic group may be saturated or unsaturated and which phenyl or heterocyclic group may be substituted with one or two substituents selected independently from oxo, hydroxy, halogeno, C_{1-3}alkyl, C_{1-3}alkoxy, C_{1-3}alkanoyloxy, trifluoromethyl, cyano, amino, nitro and C_{1-4}alkoxycarbonyl;

2) $X^2C_{2-4}alkylX^3C_{1-3}$alkyl (wherein X^2 is O or NR^{11} (wherein R^{11} is hydrogen, C_{1-3}alkyl or $C_{1-3}alkoxyC_{2-3}$alkyl) and X^3 is O, NR^{12}, S, SO or SO_2 (wherein R^{12} is hydrogen, C_{1-3}alkyl or $C_{1-3}alkoxyC_{2-3}$alkyl));

3) $C_{1-2}alkylX^4C_{2-3}alkylX^5C_{1-3}$alkyl (wherein X^4 and X^5 each independently represent O, S, SO, SO_2 or NR^{13} (wherein R^{13} is hydrogen, C_{1-3}alkyl or $C_{1-3}alkoxyC_{2-3}$alkyl)); and

4) $C_{1-3}alkylX^6C_{1-3}$alkyl (wherein X^6 is O, S, SO, SO_2 or NR^{14} (wherein R^{14} is hydrogen, C_{1-3}alkyl or $C_{1-3}alkoxyC_{2-3}$alkyl));

R^3 is hydroxy, halogeno, nitro, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, C_{1-3}alkyl, cyano, amino or $R^{15}X^7$, wherein X^7 is a direct bond, O, CH_2, S, SO, SO_2, $NR^{16}CO$, $CONR^{17}$, SO_2NR^{18}, $NR^{19}SO_2$ or NR^{20} (wherein R^{16}, R^{17}, R^{18}, R^{19} and R^{20} each independently represent hydrogen, C_{1-3}alkyl or $C_{1-3}alkoxyC_{2-3}$alkyl); and

R^{15} is selected from one of the following groups:

1) hydrogen or C_{1-5}alkyl, which may be substituted with one or more groups selected independently from hydroxy, fluoro and amino;

2) $C_{1-5}alkylX^8COR^{21}$ (wherein X^8 is O or NR^{22} (wherein R^{22} is hydrogen, C_{1-3}alkyl or $C_{1-3}alkoxyC_{2-3}$alkyl) and R^{21} is C_{1-3}alkyl, $NR^{23}R^{24}$ or OR^{25} (wherein R^{23}, R^{24} and R^{25} each independently represent hydrogen, C_{1-3}alkyl or $C_{1-3}alkoxyC_{2-3}$alkyl));

3) $C_{1-5}alkylX^9R^{26}$ (wherein X^9 is O, S, SO, SO_2, OCO, $NR^{27}CO$, $CONR^{28}$, SO_2NR^{29}, $NR^{30}SO_2$ or NR^{31} (wherein R^{27}, R^{28}, R^{29}, R^{30} and R^{31} each independently represent hydrogen, C_{1-3}alkyl or $C_{1-3}alkoxyC_{2-3}$alkyl) and R^{26} is hydrogen, C_{1-3}alkyl,

cyclopentyl, cyclohexyl or a 5 or 6 membered saturated heterocyclic group with one or two heteroatoms selected independently from O, S and N, which C_{1-3}alkyl group may be substituted with one or two substituents selected independently from oxo, hydroxy, halogeno and C_{1-4}alkoxy and which heterocyclic group may be substituted with one or two substituents selected independently from oxo, hydroxy, halogeno, C_{1-4}alkyl,

C_{1-4}hydroxyalkyl and C_{1-4}alkoxy);

4) C_{1-5}alkyl$X^{10}C_{1-5}$alkyl$X^{11}R^{32}$ (wherein X^{10} and X^{11} each independently represent O, S, SO, SO_2, $NR^{33}CO$, $CONR^{34}$, SO_2NR^{35}, $NR^{36}SO_2$ or NR^{37} (wherein R^{33}, R^{34}, R^{35}, R^{36} and R^{37} each independently represent hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{32} is hydrogen or C_{1-3}alkyl);

5) R^{38} (wherein R^{38} is a 5 or 6 membered saturated heterocyclic group with one or two heteroatoms selected independently from O, S and N, which heterocyclic group may be substituted with one or two substituents selected independently from oxo, hydroxy, halogeno, C_{1-4}alkyl, C_{1-4}hydroxyalkyl and C_{1-4}alkoxy);

6) C_{1-5}alkylR^{38} (wherein R^{38} is as defined hereinbefore);

7) C_{2-5}alkenylR^{38} (wherein R^{38} is as defined hereinbefore);

8) C_{2-5}alkynylR^{38} (wherein R^{38} is as defined hereinbefore);

9) R^{39} (wherein R^{39} is a pyridone group, a phenyl group or a 5 or 6 membered aromatic heterocyclic group with 1 to 3 heteroatoms selected independently from O, N and S, which pyridone, phenyl or heterocyclic group may carry up to 5 substituents selected independently from hydroxy halogeno, amino, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}hydroxyalkyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, C_{1-4}hydroxyalkoxy, carboxy, trifluoromethyl, cyano, $CONR^{40}R^{41}$ and $NR^{42}COR^{43}$ (wherein R^{40}, R^{41}, R^{42} and R^{43} each independently represent hydrogen, C_{1-4}alkyl or C_{1-3}alkoxyC_{2-3}alkyl));

10) C_{1-5}alkylR^{39} (wherein R^{39} is as defined hereinbefore);

11) C_{2-5}alkenylR^{39} (wherein R^{39} is as defined hereinbefore);

12) C_{2-5}alkynylR^{39} (wherein R^{39} is as defined hereinbefore);

13) C_{1-5}alkyl$X^{12}R^{39}$ (wherein X^{12} is O, S, SO, SO_2, $NR^{44}CO$, $CONR^{45}$, SO_2NR^{46}, $NR^{47}SO_2$ or NR^{48} (wherein R^{44}, R^{45}, R^{46}, R^{47} and R^{48} each independently represent hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{39} is as defined hereinbefore);

14) C_{2-5}alkenyl$X^{13}R^{39}$ (wherein X^{13} is O, S, SO, SO_2, $NR^{49}CO$, $CONR^{50}$, SO_2NR^{51}, $NR^{52}SO_2$ or NR^{53} (wherein R^{49}, R^{50}, R^{51}, R^{52} and R^{53} each independently represent hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{39} is as defined hereinbefore);

15) C_{2-5}alkynyl$X^{14}R^{39}$ (wherein X^{14} is O, S, SO, SO_2, $NR^{54}CO$, $CONR^{55}$, SO_2NR^{56}, $NR^{57}SO_2$ or NR^{58} (wherein R^{54}, R^{55}, R^{56}, R^{57} and R^{58} each independently represent hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{39} is as defined hereinbefore);

16) C_{1-3}alkyl$X^{15}C_{1-3}$alkylR^{39} (wherein X^{15} is O, S, SO, SO_2, $NR^{59}CO$, $CONR^{60}$, SO_2NR^{61}, $NR^{62}SO_2$ or NR^{6} (wherein R^{59}, R^{60}, R^{61}, R^{62} and R^{63} each independently represent hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{39} is as defined hereinbefore); and

17) C_{1-3}alkyl$X^{15}C_{1-3}$alkylR^{38} (wherein X^{15} and R^{38} are as defined hereinbefore);

n is 0, 1, 2 or 3 when Z is a 6 membered heterocyclic ring and n is 0, 1 or 2 when Z is a 5 membered heterocyclic ring;

m is 0, 1, 2, 3 or 4;

as a free base or pharmaceutically acceptable salts thereof.

According to one aspect of the present invention compounds of formula **I** may be used, wherein R^1, R^2, R^3, m and n are as defined hereinbefore; and

ring Z is a 6 membered heterocyclic ring containing 1 or 2 nitrogen atoms.

In another aspect of the invention compounds of formula **I** may be used, wherein Z is a 6 membered heterocyclic ring containing 1 or 2 nitrogen atoms and R^1 is hydrogen.

In a further aspect of the invention compounds of formula **I** may be used, wherein R^2 is halogeno, C_{1-3}alkyl, trifluoromethyl, cyano, carbamoyl, *N*-C_{1-4}alkylcarbamoyl, aminosulphonyl or a group R^4X^1,

wherein X^1 is $CONR^6R^7$ (wherein R^6 is hydrogen or C_{1-2}alkyl and R^7 is C_{1-4}alkyl and wherein R^4 is linked to R^7); and

n is 0 or 1.

In yet another aspect of the invention compounds of formula **I** may be used, wherein R^3 is $R^{15}X^7$,

wherein X^7 is O; and

R^{15} is selected from one of the following groups:

1) hydrogen or C_{1-5}alkyl;

3) C_{1-5}alkylX^9R^{26} (wherein X^9 is O (wherein R^{26} is hydrogen or C_{1-3}alkyl));

4) C_{1-5}alkyl$X^{10}C_{1-5}$alkyl$X^{11}R^{32}$ (wherein X^{10} and X^{11} are O, and R^{32} is hydrogen or C_{1-3}alkyl);

6) C_{1-5}alkylR^{38} (wherein R^{38} is a 6 membered saturated heterocyclic group with one or two heteroatoms selected independently from O, S and N, which heterocyclic group may be substituted with one or two substituents selected independently from oxo, hydroxy, halogeno, C_{1-4}alkyl, C_{1-4}hydroxyalkyl and C_{1-4}alkoxy);

7) C_{2-5}alkenylR^{38} (wherein R^{38} is as defined hereinbefore);

10) C_{1-5}alkylR^{39} (wherein R^{39} is a 5 or 6 membered aromatic heterocyclic group with 1 to 3 heteroatoms selected independently from O, N and S, which heterocyclic group may carry up to 4 substituents selected independently from hydroxy halogeno, amino, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}hydroxyalkyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, C_{1-4}hydroxyalkoxy, carboxy, trifluoromethyl, cyano, $CONR^{40}R^{41}$ and $NR^{42}COR^{43}$ (wherein R^{40}, R^{41}, R^{42} and R^{43} each independently represent hydrogen, C_{1-4}alkyl or C_{1-3}alkoxyC_{2-3}alkyl));

13) C_{1-5}alkyl$X^{12}R^{39}$ (wherein X^{12} is O and R^{39} is as defined hereinbefore);

m is 0, 1 or 2.

One aspect of the invention relates to the use of compounds of formula **I**, wherein R^1 is hydrogen, Z is a 6 membered heterocyclic ring containing 1 or 2 nitrogen atoms, R^2 is halogeno or C_{1-3}alkyl and n is 0 or 1, R^3 is morpholinopropoxy, dioxothiomorpholino-propoxy, morpholinobutenyl-oxy, pyridyloxy-ethoxy, triazolyl-ethoxy, imidazolyl-ethoxy, methoxy, methoxyethoxy or methoxyethoxy-ethoxy and m is 0, 1, or 2.

In another aspect of the invention, use is made of the following compounds in the manufacturing of a medicament for the treatment and/or prevention of conditions associated with glycogen synthase kinase-3;

4-(7-Azaoxindol-3-yl)-6-methoxy-7-(2-methoxyethoxy)quinazoline,

4-(7-Azaoxindol-3-yl)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,

4-(7-Azaoxindol-3-yl)-7-(2-(imidazol-1-yl)ethoxy)-6-methoxyquinazoline,
4-(5,7-Diaza-6-methyloxindol-3-yl)-7-(3-morpholinopropoxy)quinazoline,
4-(7-Aza-6-chlorooxindol-3-yl)-7-(3-morpholinopropoxy)quinazoline,
4-(5,7-Diaza-6-methyloxindol-3-yl)-6-methoxy-7- (2-(1,2,3-triazol-1-yl)ethoxy)quinazoline,
4-(5,7-Diaza-6-methyloxindol-3-yl)-7-(2-(2-methoxyethoxy)ethoxy)quinazoline,
4-(7-Azaoxindol-3-yl)-7-(3-morpholinopropoxy)quinazoline,
4-(7-Azaoxindol-3-yl)-7-(2-(2-methoxyethoxy)ethoxy)quinazoline,
4-(7-Azaoxindol-3-yl)-7-(4-morpholinobut-2-en-1-yloxy)quinazoline,
4-(5,7-Diaza-6-methyloxindol-3-yl)-6-methoxy-7-(2-(4-pyridyloxy)ethoxy)quinazoline,
4-(7-Aza-6-chlorooxindol-3-yl)-7-(2-(2-methoxyethoxy)ethoxy)quinazoline, and
4-(5,7-Diaza-6-methyloxindol-3-yl)-7-(3-(1,1-dioxothiomorpholino)-propoxy)quinazoline;
as a free base or pharmaceutically acceptable salts thereof.

For the avoidance of doubt it is to be understood that where in this specification a group is qualified by 'hereinbefore defined' or 'defined hereinbefore' the said group encompasses the first occurring and broadest definition as well as each and all of the preferred definitions of that group.

For the avoidance of doubt it is to be understood that in this specification 'C_{1-5}' means a carbon group having 1, 2, 3, 4 or 5 carbon atoms.

In this specification, unless stated otherwise, the term "alkyl" includes both straight and branched chain alkyl groups. C_{1-5}alkyl may be methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, i-pentyl, t-pentyl, neo-pentyl.

The term "alkoxy" as used herein, unless stated otherwise includes "alkyl"O groups in which "alkyl" is as hereinbefore defined. C_{1-5}alkoxy may be methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy, t-butoxy, n-pentyloxy, i-pentyloxy, t-pentyloxy, neo-pentyloxy.

The term "alkanoyl" as used herein, unless otherwise stated includes formyl and alkylC=O groups in which "alkyl" is as defined hereinbefore, for example C_2alkanoyl is ethanoyl and refers to $CH_3C=O$, C_1alkanoyl is formyl and refers to CHO.

In this specification, unless stated otherwise, the term "alkenyl" includes both straight and branched chain alkenyl groups but references to individual alkenyl groups such as 2-butenyl are specific for the straight chain version only. Unless otherwise stated, the term "alkenyl" advantageously refers to chains with 2 to 5 carbon atoms, preferably 3 to 4 carbon atoms.

In this specification, unless stated otherwise, the term "alkynyl" includes both straight and branched chain alkynyl groups but references to individual alkynyl groups such as 2-butynyl are specific for the straight chain version only. Unless otherwise stated, the term "alkynyl" advantageously refers to chains with 2 to carbon atoms, preferably 3 to 4 carbon atoms.

In this specification, unless stated otherwise, the term "5 or 6 membered heterocyclic group with one or two heteroatoms, selected independently from O, S and N, which heterocyclic group may be saturated or unsaturated" or "5 or 6 membered heterocyclic ring containing 1 to 3 heteroatoms selected independently from O, N and S, which heterocyclic group may be saturated or unsaturated", includes both heteroaromatic rings and heterocyclic rings that are saturated. Examples of such heterocyclic groups includes, but are not limited to furyl, imidazolyl, isoxazolyl, isothiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, thiazolyl, thienyl, imidazolidinyl, imidazolinyl, morpholinyl, piperazinyl, piperidyl, piperidonyl, pyrazolidinyl, pyrazolinyl, pyrrolidinyl, pyrrolinyl, tetrahydropyranyl or thiomorpholinyl.

In this specification, unless stated otherwise, the term "5 or 6 membered saturated heterocyclic group with one or two heteroatoms, selected independently from O, S and N" may be, but are not limited to imidazolidinyl, imidazolinyl, morpholinyl, piperazinyl, piperidyl, piperidonyl, pyrazolidinyl, pyrazolinyl, pyrrolidinyl, pyrrolinyl, tetrahydropyranyl or thiomorpholinyl.

In this specification, unless stated otherwise, the term "5 or 6 membered aromatic heterocyclic group with 1 to 3 heteroatoms, selected independently from O, N and S" may be, but are not limited to furyl, imidazolyl, isoxazolyl, isothiazolyl, oxazolyl, pyrazinyl, triazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, thiazolyl or thienyl.

In this specification, unless stated otherwise, the term "5 or 6 membered heterocyclic ring containing 1 to 3 heteroatoms selected independently from O, N and S" may be, but are not

limited to furyl, imidazolyl, isoxazolyl, isothiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, thiazolyl or thienyl.

In this specification, unless stated otherwise, the term halogeno may be fluor, chlorine, bromine or iodine.

For the avoidance of any doubt, it is to be understood that when X^7 is, for example, a group of formula $NR^{16}CO$, it is the nitrogen atom be substituted withing the R^{16} group which is attached to the quinazoline ring and the carbonyl (CO) group is attached to R^{15}, whereas when X^7 is, for example, a group of formula $CONR^{17}$, it is the carbonyl group which is attached to the quinazoline ring and the nitrogen atom be substituted withing the R^{17} group is attached to R^{15}. A similar convention applies to the other two atoms X^7 linking groups such as $NR^{19}SO_2$ and SO_2NR^{18}. When X^7 is NR^{20} it is the nitrogen atom be substituted withing the R^{20} group, which is linked to the quinazoline ring and to R^{15}. An analogous convention applies to other groups. It is further to be understood that when X^7 represents NR^{20} and R^{20} is $C_{1-3}alkoxyC_{2-3}alkyl$ it is the $C_{2-3}alkyl$ moiety, which is linked to the nitrogen atom of X^7 and an analogous convention applies to other groups.

For the avoidance of any doubt, it is to be understood that in a compound of formula **I** when R^{15} is, for example, a group of formula $C_{1-5}alkylX^{15}C_{1-5}alkylR^{39}$, it is the terminal $C_{1-5}alkyl$ moiety, which is linked to X^{15}, similarly when R^{15} is, for example, a group of formula $C_{2-5}alkenylR^{39}$ it is the $C_{2-5}alkenyl$ moiety, which is linked to X^7 and an analogous convention applies to other groups.

For the avoidance of any doubt, it is to be understood that when R^{39} carries a $C_{1-4}aminoalkyl$ substituent it is the $C_{1-4}alkyl$ moiety, which is attached to R^{39} whereas when R^{39} carries a $C_{1-4}alkylamino$ substituent it is the amino moiety, which is attached to R^{39} and an analogous convention applies to other groups.

For the avoidance of any doubt when X^1 is $C_{2-4}alkanoyl$ it is the carbonyl moiety, which is linked to the heteroaromatic oxindole group and it is the alkyl moiety, which is linked to R^4 and an analogous convention applies to other groups.

For the avoidance of any doubt when R^2 is a group $X^2C_{2-4}alkylX^3C_{1-3}alkyl$ it is X^2, which is linked to the heteroaromatic oxindole group and an analogous convention applies to other groups. When R^2 is a group $C_{1-2}alkylX^4C_{2-3}alkylX^5C_{1-3}alkyl$ it is the $C_{1-2}alkyl$

moiety, which is linked to the heteroaromatic oxindole group and an analogous convention applies to other groups.

Some compounds of formula **I** may have chiral centres and/or geometric isomeric centres (E- and Z- isomers), and it is to be understood that the invention encompasses all such optical, diastereoisomers and geometric isomers that possess GSK3 inhibitory activity.

It is to be understood that the present invention also relates to any and all tautomeric forms of the compounds of formula **I**.

The present invention relates to the use of compounds of formula **I** as hereinbefore defined as well as to the salts thereof. Salts for use in pharmaceutical compositions will be. pharmaceutically acceptable salts, but other salts may be useful in the production of the compounds of formula **I**.

Both organic and inorganic acids can be employed to form non-toxic pharmaceutically acceptable acid addition salts of the compounds of this invention. In addition, a suitable pharmaceutically acceptable salt of the compounds of the invention is an alkali metal salt, an alkaline earth metal salt or a salt with an organic base.

Compound of formula **I**, or salt thereof, may be prepared by any process known to be applicable to the preparation of chemically-related compounds. Such processes include, for example, those illustrated in European Patent Applications Publication Nos. 0520722, 0566226, 0602851, 0635498 and 0636608 and PCT application WO 99/10349.

Pharmaceutical composition

According to one aspect of the present invention there is provided a pharmaceutical composition comprising a compound of formula **I**, as a free base or salts thereof, for use in prevention and/or treatment of dementia related diseases, Alzheimer's Disease and conditions associated with glycogen synthase kinase-3 and other conditions listed below.

The composition may be in a form suitable for oral administration, for example as a tablet,

pill, syrup, powder, granule or capsule, for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) as a sterile solution, suspension or emulsion, for topical administration as an ointment, patch or cream or for rectal administration as a suppository.

In general the above compositions may be prepared in a conventional manner using pharmaceutically acceptable carriers or diluents.

Suitable daily doses of the compounds of formula **I** in the treatment of a mammal, including man, are approximately 0.01 to 250 mg/kg bodyweight at peroral administration and about 0.001 to 250 mg/kg bodyweight at parenteral administration. The typical daily dose of the active ingredients varies within a wide range and will depend on various factors such as the relevant indication, the route of administration, the age, weight and sex of the patient and may be determined by a physician.

Illustrate representative pharmaceutical dosage forms containing a compound of formula **I**, as a free base or salts thereof, are described in WO 99/10349.

Medical use

Surprisingly, it has been found that the compounds defined in the present invention, as a free base or salts thereof, are useful in therapy. The compounds of the present invention are well suited for inhibiting glycogen synthase kinase-3 (GSK3). Accordingly, the compounds of the present invention are expected to be useful in the prevention and/or treatment of conditions associated with glycogen synthase kinase-3 activity, i.e. the compounds may be used to produce an inhibitory effect of GSK3 in mammals, including man, in need of such prevention and/or treatment.

GSK3 is highly expressed in the central and peripheral nervous system and in other tissues. Thus, it is expected that compounds of the invention are well suited for the prevention and/or treatment of conditions associated with glycogen synthase kinase-3 in the central and peripheral nervous system. In particular, the compounds of the invention are expected to be suitable in the manufacture of a medicament for the prevention and/or treatment of dementia related diseases and Alzheimer's Disease.

The dementia related diseases are selected from the group consisting of Frontotemporal dementia Parkinson's Type, Parkinson dementia complex of Guam, HIV dementia, diseases with associated neurofibrillar tangle pathologies, predemented states, vascular dementia, dementia with Lewy bodies, Frontotemporal dementia and dementia pugilistica. The compounds of the invention are also expected to be suitable in the manufacture of a medicament for the prevention and/or treatment of amyotrophic lateral sclerosis, corticobasal degeneration, Down syndrome, Huntington's Disease, Parkinson's Disease, postencephelatic parkinsonism, progressive supranuclear palsy, Pick's Disease, Niemann-Pick's Disease, stroke, head trauma and other chronic neurodegenerative diseases, Bipolar Disease, affective disorders, depression, schizophrenia, cognitive disorders, hair loss and contraceptive medication.

The compounds of the invention are further expected to be suitable in the manufacture of a medicament for the prevention and/or treatment of Mild Cognitive Impairment, Age-Associated Memory Impairment, Age-Related Cognitive Decline, Cognitive Impairement No Dementia, mild cognitive decline, mild neurocognitive decline, Late-Life Forgetfulness, memory impairment and cognitive impairment and androgenetic alopecia.

The present invention relates also to the use of a compound of formula **I** as defined hereinbefore, in the manufacture of a medicament for the prevention and/or treatment of conditions associated with glycogen synthase kinase-3.

The invention also provides for a method of prevention and/or treatment of dementia related diseases, Alzheimer's Disease and conditions associated with glycogen synthase kinase-3 and other conditions listed above comprising administrering to a mammal, including man, in need of such prevention and/or treatment a therapeutically effective amount of a compound of formula **I**, as hereinbefore defined.

In the context of the present specification, the term "therapy" also includes "prevention" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

Non- Medical use

In addition to their use in therapeutic medicine, the compounds of formula **I** as a free base or salts thereof, are also useful as pharmacological tools in the development and standardisation of *in vitro* and *in vivo* test systems for the evaluation of the effects of inhibitors of GSK3 related activity in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutics agents.

Pharmacology

Determination of ATP competition in Scintillation Proximity GSK3β Assay.

GSK3β scintillation proximity assay.

The competition experiments were carried out in duplicate with 10 different concentrations of the inhibitors in clear-bottom microtiter plates (Wallac, Finland). A biotinylated peptide substrate, Biotin-Ala-Ala-Glu-Glu-Leu-Asp-Ser-Arg-Ala-Gly-Ser(PO_3H_2)-Pro-Gln-Leu (AstraZeneca, Lund), was added at a final concentration of 1 μM in an assay buffer containing 1 mU recombinant human GSK3β (Dundee University, UK), 12 mM morpholinepropanesulfonic acid (MOPS), pH 7.0, 0.3 mM EDTA, 0.01% β-mercaptorethanol, 0.004 % Brij 35 (a natural detergent), 0.5 % glycerol and 0.5 μg BSA/25 μl. The reaction was initiated by the addition of 0.04 μCi [γ-^{33}P]ATP (Amersham, UK) and unlabelled ATP at a final concentration of 1 μM and assay volume of 25 μl. After incubation for 20 minutes at room temperature, each reaction was terminated by the addition of 25 μl stop solution containing 5 mM EDTA, 50 μM ATP, 0.1 % Triton X-100 and 0.25 mg streptavidin coated Scintillation Proximity Assay (SPA) beads (Amersham, UK). After 6 hours the radioactivity was determined in a liquid scintillation counter (1450 MicroBeta Trilux, Wallac). The inhibition curves were analysed by non-linear regression using GraphPad Prism, USA. The K_m value of ATP for GSK3β, used to calculate the inhibition constants (K_i) of the various compounds, was 20 μM.

The following abbreviations have been used:

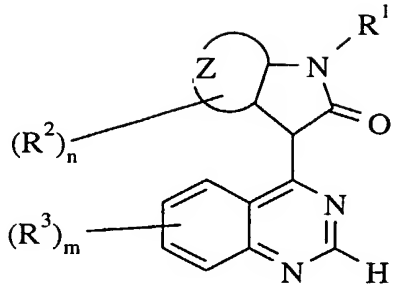
ATP	Adenosine Triphophatase
BSA	Bovin Serum Albumin
EDTA	Ethylenediaminetetraacetic acid
GSK3	Glycogen synthase kinase 3
MOPS	Morpholinepropanesulfonic acid
SPA	Scintillation Proximity Assay

Results

Typical K_i values for the compounds of the present invention are in the range of about 0.001 to about 10,000 nM. Other values for K_i are in the range of about 0.001 to about 1000 nM. Further values for K_i are in the range of about 0.001 nM to about 300 nM.

CLAIMS

1. Use of a compound of formula **I**



(I)

wherein:

ring Z is a 5 or 6 membered heterocyclic ring containing 1 to 3 heteroatoms selected independently from O, N and S but not more than 2 nitrogen atom;

R^1 is hydrogen or C_{1-3}alkyl;

R^2 is hydroxy, halogeno, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, 2,2,2-trifluoroethyl, cyano, amino, nitro, C_{1-3}alkyl, C_{1-3}alkoxy, C_{1-3}alkanoyloxy, C_{2-4}alkanoyl, C_{1-4}alkanoylamino, C_{1-4}alkoxycarbonyl, C_{1-4}alkylthio, C_{1-4}alkylsulphinyl, C_{1-4}alkylsulphonyl, carbamoyl,*N*-C_{1-4}alkylcarbamoyl, *N*,*N*-di(C_{1-4}alkyl)carbamoyl, aminosulphonyl, *N*-C_{1-4}alkylaminosulphonyl, *N*,*N*-di(C_{1-4}alkyl)aminosulphonyl or C_{1-4}alkylsulphonylamino, or

R^2 is selected from one of the following groups:

1) R^4X^1, wherein X^1 is a direct bond, O, NR^5, C_{1-3}alkyl, C_{2-4}alkanoyl, $CONR^6R^7$, $SO_2NR^8R^9$ or SO_2R^{10} (wherein R^5, R^6 and R^8 each independently represent hydrogen or C_{1-2}alkyl and R^7, R^9 and R^{10} each independently represent C_{1-4}alkyl and wherein R^4 is linked to R^7, R^9 or R^{10}); and

R^4 is phenyl or a 5 or 6 membered heterocyclic group with one or two heteroatoms, selected independently from O, S and N, which heterocyclic group may be saturated or unsaturated and which phenyl or heterocyclic group may be substituted with one

or two substituents selected independently from oxo, hydroxy, halogeno, C_{1-3}alkyl, C_{1-3}alkoxy, C_{1-3}alkanoyloxy, trifluoromethyl, cyano, amino, nitro and C_{1-4}alkoxycarbonyl;

2) $X^2C_{2-4}alkylX^3C_{1-3}alkyl$ (wherein X^2 is O or NR^{11} (wherein R^{11} is hydrogen, C_{1-3}alkyl or $C_{1-3}alkoxyC_{2-3}alkyl$) and X^3 is O, NR^{12}, S, SO or SO_2 (wherein R^{12} is hydrogen, C_{1-3}alkyl or $C_{1-3}alkoxyC_{2-3}alkyl$));

3) $C_{1-2}alkylX^4C_{2-3}alkylX^5C_{1-3}alkyl$ (wherein X^4 and X^5 each independently represent O, S, SO, SO_2 or NR^{13} (wherein R^{13} is hydrogen, C_{1-3}alkyl or $C_{1-3}alkoxyC_{2-3}alkyl$)); and

4) $C_{1-3}alkylX^6C_{1-3}alkyl$ (wherein X^6 is O, S, SO, SO_2 or NR^{14} (wherein R^{14} is hydrogen, C_{1-3}alkyl or $C_{1-3}alkoxyC_{2-3}alkyl$));

R^3 is hydroxy, halogeno, nitro, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, C_{1-3}alkyl, cyano, amino or $R^{15}X^7$, wherein X^7 is a direct bond, O, CH_2, S, SO, SO_2, $NR^{16}CO$, $CONR^{17}$, SO_2NR^{18}, $NR^{19}SO_2$ or NR^{20} (wherein R^{16}, R^{17}, R^{18}, R^{19} and R^{20} each independently represent hydrogen, C_{1-3}alkyl or $C_{1-3}alkoxyC_{2-3}alkyl$); and

R^{15} is selected from one of the following groups:

1) hydrogen or C_{1-5}alkyl, which may be substituted with one or more groups selected independently from hydroxy, fluoro and amino;

2) $C_{1-5}alkylX^8COR^{21}$ (wherein X^8 is O or NR^{22} (wherein R^{22} is hydrogen, C_{1-3}alkyl or $C_{1-3}alkoxyC_{2-3}alkyl$) and R^{21} is C_{1-3}alkyl, $NR^{23}R^{24}$ or OR^{25} (wherein R^{23}, R^{24} and R^{25} each independently represent hydrogen, C_{1-3}alkyl or $C_{1-3}alkoxyC_{2-3}alkyl$));

3) $C_{1-5}alkylX^9R^{26}$ (wherein X^9 is O, S, SO, SO_2, OCO, $NR^{27}CO$, $CONR^{28}$, SO_2NR^{29}, $NR^{30}SO_2$ or NR^{31} (wherein R^{27}, R^{28}, R^{29}, R^{30} and R^{31} each independently represent hydrogen, C_{1-3}alkyl or $C_{1-3}alkoxyC_{2-3}alkyl$) and R^{26} is hydrogen, C_{1-3}alkyl, cyclopentyl, cyclohexyl or a 5 or 6 membered saturated heterocyclic group with one or two heteroatoms selected independently from O, S and N, which C_{1-3}alkyl group may be substituted with one or two substituents selected independently from oxo, hydroxy, halogeno and C_{1-4}alkoxy and which heterocyclic group may be substituted with one or two substituents selected independently from oxo, hydroxy, halogeno, C_{1-4}alkyl,

C_{1-4}hydroxyalkyl and C_{1-4}alkoxy);

4) C_{1-5}alkyl$X^{10}C_{1-5}$alkyl$X^{11}R^{32}$ (wherein X^{10} and X^{11} each independently represent O, S, SO, SO_2, $NR^{33}CO$, $CONR^{34}$, SO_2NR^{35}, $NR^{36}SO_2$ or NR^{37} (wherein R^{33}, R^{34}, R^{35}, R^{36} and R^{37} each independently represent hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{32} is hydrogen or C_{1-3}alkyl);

5) R^{38} (wherein R^{38} is a 5 or 6 membered saturated heterocyclic group with one or two heteroatoms selected independently from O, S and N, which heterocyclic group may be substituted with one or two substituents selected independently from oxo, hydroxy, halogeno, C_{1-4}alkyl, C_{1-4}hydroxyalkyl and C_{1-4}alkoxy);

6) C_{1-5}alkylR^{38} (wherein R^{38} is as defined hereinbefore);

7) C_{2-5}alkenylR^{38} (wherein R^{38} is as defined hereinbefore);

8) C_{2-5}alkynylR^{38} (wherein R^{38} is as defined hereinbefore);

9) R^{39} (wherein R^{39} is a pyridone group, a phenyl group or a 5 or 6 membered aromatic heterocyclic group with 1 to 3 heteroatoms selected independently from O, N and S, which pyridone, phenyl or heterocyclic group may carry up to 5 substituents selected independently from hydroxy halogeno, amino, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}hydroxyalkyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, C_{1-4}hydroxyalkoxy, carboxy, trifluoromethyl, cyano, $CONR^{40}R^{41}$ and $NR^{42}COR^{43}$ (wherein R^{40}, R^{41}, R^{42} and R^{43} each independently represent hydrogen, C_{1-4}alkyl or C_{1-3}alkoxyC_{2-3}alkyl));

10) C_{1-5}alkylR^{39} (wherein R^{39} is as defined hereinbefore);

11) C_{2-5}alkenylR^{39} (wherein R^{39} is as defined hereinbefore);

12) C_{2-5}alkynylR^{39} (wherein R^{39} is as defined hereinbefore);

13) C_{1-5}alkyl$X^{12}R^{39}$ (wherein X^{12} is O, S, SO, SO_2, $NR^{44}CO$, $CONR^{45}$, SO_2NR^{46}, $NR^{47}SO_2$ or NR^{48} (wherein R^{44}, R^{45}, R^{46}, R^{47} and R^{48} each independently represent hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{39} is as defined hereinbefore);

14) C_{2-5}alkenyl$X^{13}R^{39}$ (wherein X^{13} is O, S, SO, SO_2, $NR^{49}CO$, $CONR^{50}$, SO_2NR^{51}, $NR^{52}SO_2$ or NR^{53} (wherein R^{49}, R^{50}, R^{51}, R^{52} and R^{53} each independently represent hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{39} is as defined hereinbefore);

15) C_{2-5}alkynyl$X^{14}R^{39}$ (wherein X^{14} is O, S, SO, SO_2, $NR^{54}CO$, $CONR^{55}$, SO_2NR^{56}, $NR^{57}SO_2$ or NR^{58} (wherein R^{54}, R^{55}, R^{56}, R^{57} and R^{58} each independently represent hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{39} is as defined hereinbefore);

16) C_{1-3}alkyl$X^{15}C_{1-3}$alkylR^{39} (wherein X^{15} is O, S, SO, SO_2, $NR^{59}CO$, $CONR^{60}$, SO_2NR^{61}, $NR^{62}SO_2$ or NR^{6} (wherein R^{59}, R^{60}, R^{61}, R^{62} and R^{63} each independently

represent hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{39} is as defined hereinbefore); and

17) C_{1-3}alkyl$X^{15}C_{1-3}$alkylR^{38} (wherein X^{15} and R^{38} are as defined hereinbefore);

n is 0, 1, 2 or 3 when Z is a 6 membered heterocyclic ring and n is 0, 1 or 2 when Z is a 5 membered heterocyclic ring;

m is 0, 1, 2, 3 or 4;

as a free base or pharmaceutically acceptable salts thereof, in the manufacturing of a medicament for the treatment and/or prevention of conditions associated with glycogen synthase kinase-3.

2. The use of a compound according to claim 1, wherein Z is a 6 membered heterocyclic ring containing 1 or 2 nitrogen atoms and R^1 is hydrogen.

3. The use of a compound according to any one of claims 1 and 2, wherein R^2 is halogeno, C_{1-3}alkyl, trifluoromethyl, cyano, carbamoyl, *N*-C_{1-4}alkylcarbamoyl, aminosulphonyl or a group R^4X^1,

wherein X^1 is $CONR^6R^7$ (wherein R^6 is hydrogen or C_{1-2}alkyl and R^7 is C_{1-4}alkyl and wherein R^4 is linked to R^7); and

n is 0 or 1.

4. The use of a compound according to any one of claims 1 to 3,

wherein R^3 is $R^{15}X^7$,

wherein X^7 is O; and

R^{15} is selected from one of the following groups:

1) hydrogen or C_{1-5}alkyl;

3) C_{1-5}alkylX^9R^{26} (wherein X^9 is O (wherein R^{26} is hydrogen or C_{1-3}alkyl));

4) C_{1-5}alkyl$X^{10}C_{1-5}$alkyl$X^{11}R^{32}$ (wherein X^{10} and X^{11} are O, and R^{32} is hydrogen or C_{1-3}alkyl);

6) C_{1-5}alkylR^{38} (wherein R^{38} is a 6 membered saturated heterocyclic group with one or two heteroatoms selected independently from O, S and N, which heterocyclic group may be substituted with one or two substituents selected independently from oxo, hydroxy, halogeno, C_{1-4}alkyl, C_{1-4}hydroxyalkyl and C_{1-4}alkoxy);

7) C_{2-5}alkenylR^{38} (wherein R^{38} is as defined hereinbefore);

10) C_{1-5}alkylR^{39} (wherein R^{39} is a 5 or 6 membered aromatic heterocyclic group with 1 to 3 heteroatoms selected independently from O, N and S, which heterocyclic group may carry up to 4 substituents selected independently from hydroxy halogeno, amino, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}hydroxyalkyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, C_{1-4}hydroxyalkoxy, carboxy, trifluoromethyl, cyano, $CONR^{40}R^{41}$ and $NR^{42}COR^{43}$ (wherein R^{40}, R^{41}, R^{42} and R^{43} each independently represent hydrogen, C_{1-4}alkyl or C_{1-3}alkoxyC_{2-3}alkyl));

13) C_{1-5}alkyl$X^{12}R^{39}$ (wherein X^{12} is O and R^{39} is as defined hereinbefore);

m is 0, 1 or 2.

5. The use according to any one of claims 1 to 4, wherein the compounds are selected from
4-(7-Azaoxindol-3-yl)-6-methoxy-7-(2-methoxyethoxy)quinazoline,
4-(7-Azaoxindol-3-yl)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,
4-(7-Azaoxindol-3-yl)-7-(2-(imidazol-1-yl)ethoxy)-6-methoxyquinazoline,
4-(5,7-Diaza-6-methyloxindol-3-yl)-7-(3-morpholinopropoxy)quinazoline,
4-(7-Aza-6-chlorooxindol-3-yl)-7-(3-morpholinopropoxy)quinazoline,
4-(5,7-Diaza-6-methyloxindol-3-yl)-6-methoxy-7-(2-(1,2,3-triazol-1-yl)ethoxy)quinazoline,
4-(5,7-Diaza-6-methyloxindol-3-yl)-7-(2-(2-methoxyethoxy)ethoxy)quinazoline,
4-(7-Azaoxindol-3-yl)-7-(3-morpholinopropoxy)quinazoline,
4-(7-Azaoxindol-3-yl)-7-(2-(2-methoxyethoxy)ethoxy)quinazoline,
4-(7-Azaoxindol-3-yl)-7-(4-morpholinobut-2-en-1-yloxy)quinazoline,
4-(5,7-Diaza-6-methyloxindol-3-yl)-6-methoxy-7-(2-(4-pyridyloxy)ethoxy)quinazoline,
4-(7-Aza-6-chlorooxindol-3-yl)-7-(2-(2-methoxyethoxy)ethoxy)quinazoline, and
4-(5,7-Diaza-6-methyloxindol-3-yl)-7-(3-(1,1-dioxothiomorpholino)-propoxy)quinazoline;
as a free base or pharmaceutically acceptable salts thereof.

6. The use of a compound of formula **I** as defined in claim 1, in the manufacture of a medicament for the prevention and/or treatment of dementia related diseases and Alzheimer's Disease.

7. The use according to claim 6, wherein the dementia related diseases are selected from the group consisting of Frontotemporal dementia Parkinson's Type, Parkinson dementia complex of Guam, HIV dementia, diseases with associated neurofibrillar tangle pathologies, predemented states, vascular dementia, dementia with Lewy bodies, Frontotemporal dementia and dementia pugilistica.

8. The use of a compound of formula **I** as defined in claim 1, in the manufacture of a medicament for the prevention and/or treatment of amyotrophic lateral sclerosis, corticobasal degeneration, Down syndrome, Huntington's Disease, Parkinson's Disease, postencephelatic parkinsonism, progressive supranuclear palsy, Pick's Disease, Niemann-Pick's Disease, stroke, head trauma and other chronic neurodegenerative diseases, Bipolar Disease, affective disorders, depression, schizophrenia, cognitive disorders, hair loss and contraceptive medication.

9. The use of a compound of formula I as defined in claim 1, in the manufacture of a medicament for the prevention and/or treatment of Mild Cognitive Impairment, Age-Associated Memory Impairment, Age-Related Cognitive Decline, Cognitive Impairement No Dementia, mild cognitive decline, mild neurocognitive decline, Late-Life Forgetfulness, memory impairment and cognitive impairment and androgenetic alopecia.

10. A pharmaceutical composition for use in prevention and/or treatment of dementia related diseases, Alzheimer's Disease and conditions associated with glycogen synthase kinase-3, comprising a therapeutically effective amount of a compound of formula **I** as defined in any one of claim 1 to 5 and pharmaceutically acceptable carriers or diluents.

11. A method of prevention and/or treatment of dementia related diseases, Alzheimer's Disease and conditions associated with glycogen synthase kinase-3, comprising administrering to a mammal, including man in need of such treatment and/or prevention a therapeutically effective amount of a compound of formula **I** as defined in any one of claims 1 to 5.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 02/02372

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/517, A61P 25/28, A61P 25/14, A61P 25/18, A61P 25/24, A61P 9/10, A61P 15/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CHEM. ABS DATA, WPI DATA, EPO-INTERNAL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9910349 A1 (ZENECA LIMITED), 4 March 1999 (04.03.99) --	1-5,10-11
X	WO 9742187 A1 (ZENECA LIMITED), 13 November 1997 (13.11.97) --	1-5,10-11
P,X	J. Med. Chem., Volume 45, 2002, Piyasena Hewawasam et al: "Synthesis and Structure-Activity Relationships of 3-Aryloxindoles: A New Class of Calcium-Dependent, Large Conductance Potassium (Maxi-K) Channel Openers with Neuroprotective Properties", page 1487 - page 1499 --	

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 March 2003	25 -03- 2003
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Viveca Norén/EÖ Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 02/02372

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 1136493 A1 (SANOFI-SYNTHELABO), 26 Sept 2001 (26.09.01) --	1-11
A	WO 9533750 A1 (PFIZER INC.), 14 December 1995 (14.12.95) --	1-11
A	WO 0010975 A1 (SUMITOMO PHARMACEUTICALS CO., LTD.), 2 March 2000 (02.03.00) --	1-11

INTERNATIONAL SEARCH REPORT

Intern l application No.
PCT/SE02/02372

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 11
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Interna l application No.
PCT/SE02/02372

Claim 11 relates to a method of treatment of the human or animal body by surgery or by therapy/a diagnostic method practised on the human or animal body/Rule 39.1(iv). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

Information on patent family members

30/12/02

International application No.
PCT/SE 02/02372

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9910349 A1	04/03/99	AU 8816298 A	16/03/99
		EP 1005470 A	07/06/00
		JP 2001514182 T	11/09/01
		US 6294532 B	25/09/01
WO 9742187 A1	13/11/97	AU 2647597 A	26/11/97
		EP 0912557 A	06/05/99
		GB 9707800 D	00/00/00
		JP 2000510115 T	08/08/00
		US 6265411 B	24/07/01
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EP 1136493 A1	26/09/01	AU 6215001 A	03/10/01
		WO 0170728 A	27/09/01
WO 9533750 A1	14/12/95	AT 196295 T	15/09/00
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		DK 764166 T	09/10/00
		EP 0764166 A,B	26/03/97
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		IL 139504 D	00/00/00
		IL 139505 D	00/00/00
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INTERNATIONAL SEARCH REPORT

Information on patent family members

30/12/02

International application No.
PCT/SE 02/02372

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		CA 2340701 A	02/03/00
		CN 1313853 T	19/09/01
		EP 1105376 A	13/06/01
		JP 2002523400 T	30/07/02